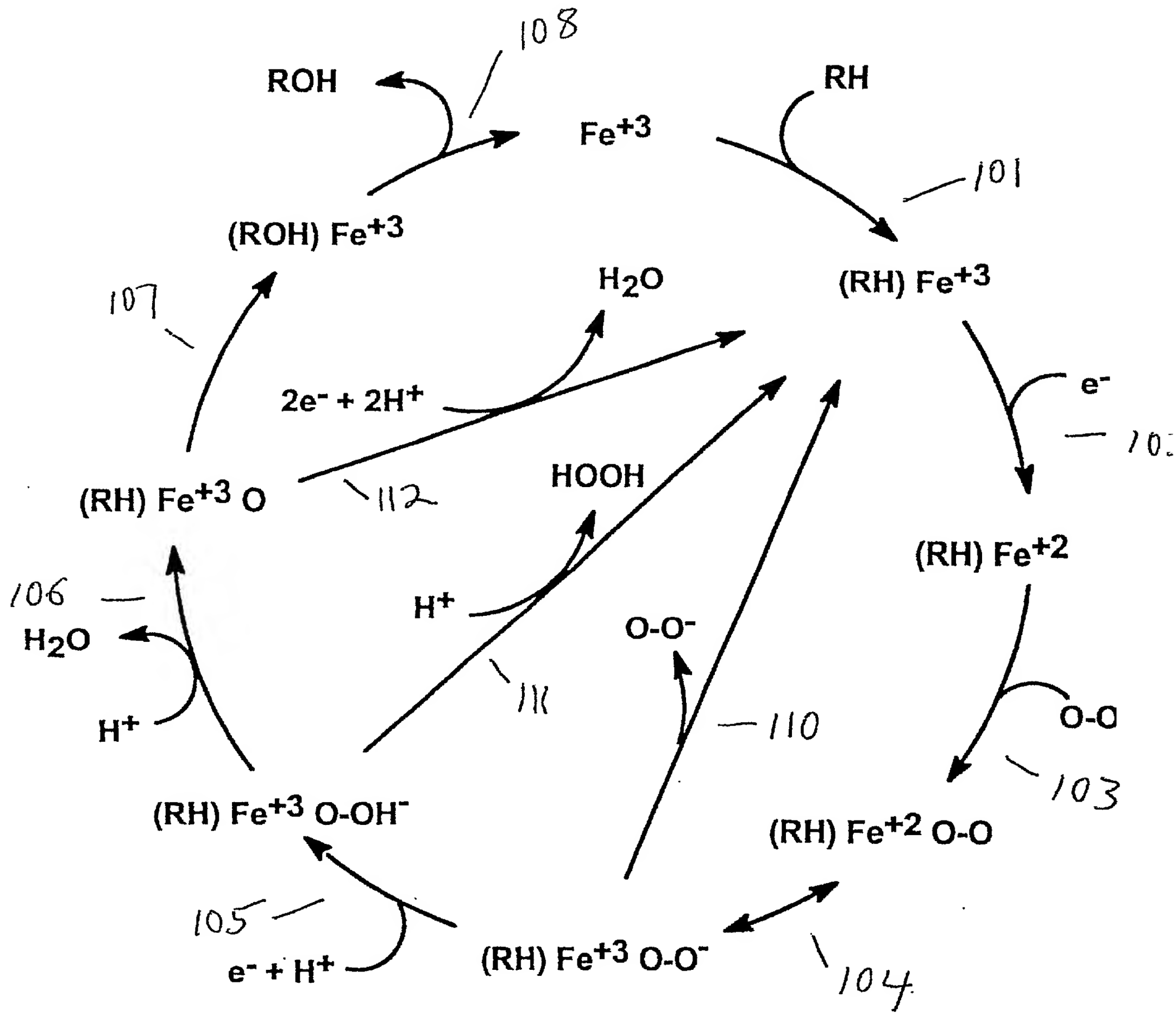

ROH
108
Fe+3
RH
(ROH) Fe+3
101
H2O
(RH) Fe+3
107
2e- + 2H+
e-
(RH) Fe+3 O
112
HOOH
(RH) Fe+2
106
H+
H2O
H+
O-O-
111
110
O-O
103
(RH) Fe+3 O-OH-
(RH) Fe+2 O-O
105
e- + H+
(RH) Fe+3 O-O-
104

FIGURE 1

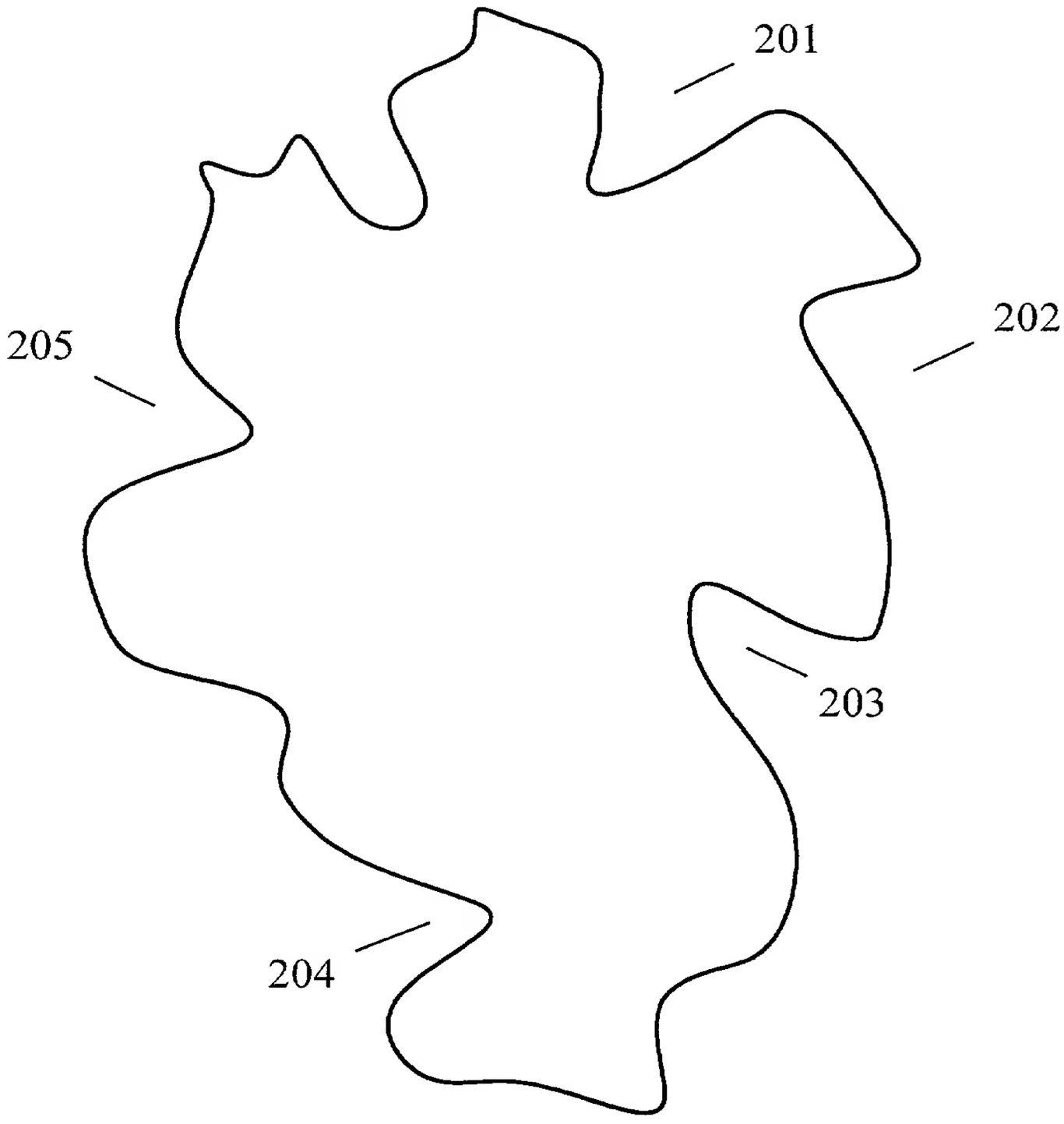


FIGURE 2

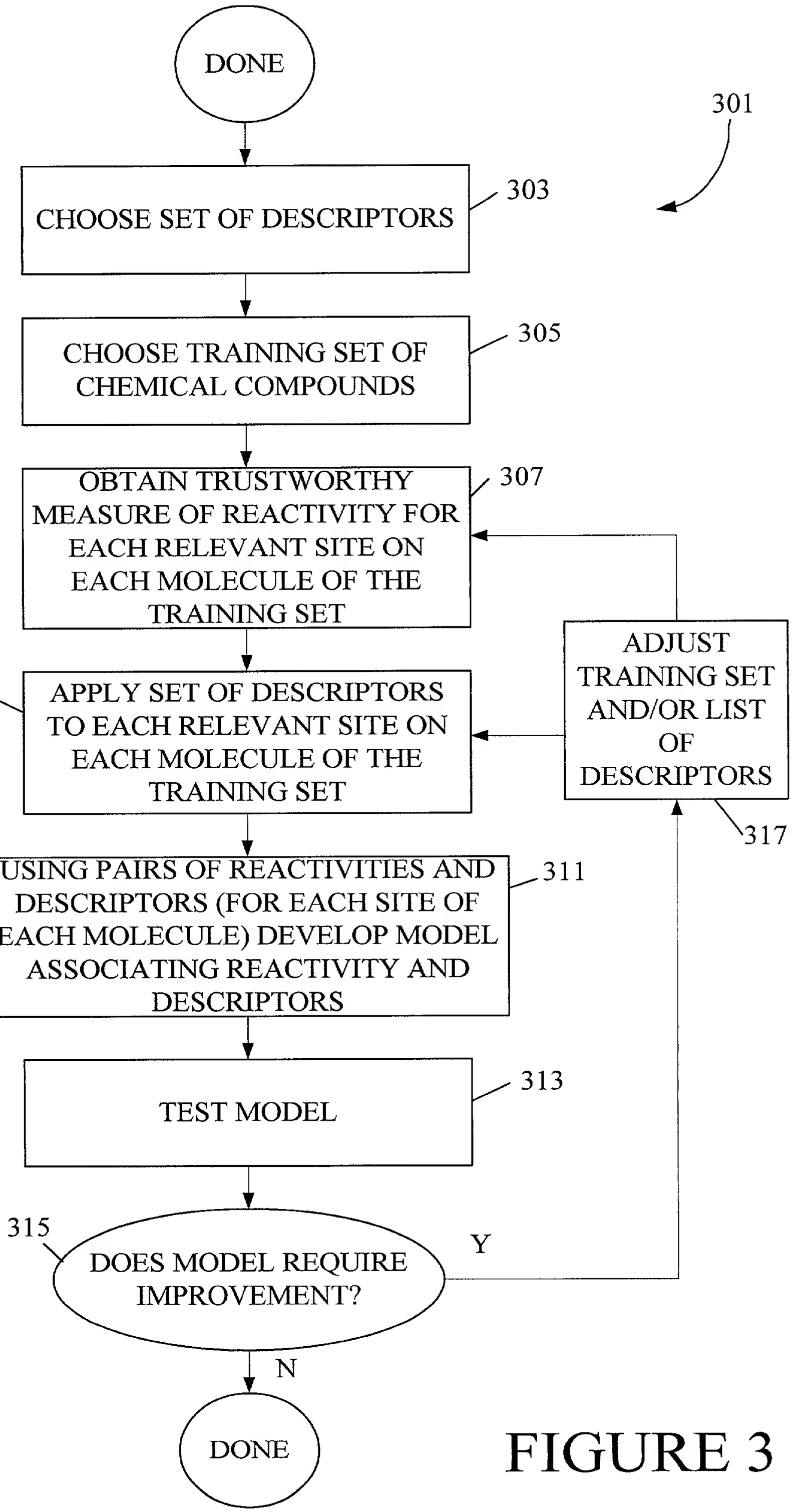

DONE
301
CHOOSE SET OF DESCRIPTORS
303
CHOOSE TRAINING SET OF CHEMICAL COMPOUNDS
305
OBTAIN TRUSTWORTHY MEASURE OF REACTIVITY FOR EACH RELEVANT SITE ON EACH MOLECULE OF THE TRAINING SET
307
309
APPLY SET OF DESCRIPTORS TO EACH RELEVANT SITE ON EACH MOLECULE OF THE TRAINING SET
ADJUST TRAINING SET AND/OR LIST OF DESCRIPTORS
317
USING PAIRS OF REACTIVITIES AND DESCRIPTORS (FOR EACH SITE OF EACH MOLECULE) DEVELOP MODEL ASSOCIATING REACTIVITY AND DESCRIPTORS
311
TEST MODEL
313
315
DOES MODEL REQUIRE IMPROVEMENT?
Y
N
DONE

FIGURE 3

Aliphatic Model Descriptors

Charge	Partial charge calculated using PEOE method
ConjSys	Size of the conjugated system (aromatic + double bond systems)
ConjSysEn	Total electronegativity values of immediate atom neighbors of the conjugated system
ConjSysPC	Total partial charge values of immediate atom neighbors of the conjugated system
Fused	Flag for whether the site is between fused rings
FuseStrain	A strain value of the fused system
3 Ring	In a 3-member ring
4 Ring	In a 4-member ring
5 Ring	In a 5-member ring
6 Ring	In a 6-member ring
Dibenzylic	Attached to two aromatic system
C	Count of carbon neighbors
Aro C	Count of aromatic carbon neighbors
Dbl C	Count of double bonded carbon neighbors
N	Count of nitrogen neighbors
O	Count of oxygen neighbors
Si	Count of silicon neighbors
S	Count of sulfur neighbors
C Ch	Sum of partial charge of carbon neighbors
Aro C Ch	Sum of partial charge of aromatic carbon neighbors
Dbl C Ch	Sum of partial charge of double bonded carbon neighbors
N Ch	Sum of partial charge of nitrogen neighbors
O Ch	Sum of partial charge of oxygen neighbors
Si Ch	Sum of partial charge of silicon neighbors
S Ch	Sum of partial charge of sulfur neighbors
Eneg	Electronegativity
H	Count of hydrogen neighbors
Tpl C	Count of triple bonded carbon neighbors
Conj N	Count of conjugated nitrogen neighbors
Aro N	Count of aromatic nitrogen neighbors
Halide	Count of halide neighbors
2 Neighbor	Count of neighbor atoms with 2 neighbors
3 Neighbor	Count of neighbor atoms with 3 neighbors
N pi	Count of nitrogen bonded to an sp2 atom
N E-neg	Count of nitrogen bonded to an electronegative atom
Amide N Side	Count of nitrogen bonded to an amide
N S-Adjacent	Count of nitrogen-sulfur fragment
O pi	Count of fragments of oxygen bonded to an sp2 atom
Aro Ether	Count of aromatic ether group
Oxy Ester	Count of oxy-ester group
Oxide	Count of generic oxide group
O E-neg	Count of fragments of oxygen bonded to an electronegative atom
S E-neg	Count of fragments of sulfur bonded to an electronegative atom
S 2 E-neg	Count of fragments of sulfur bonded to two electronegative atom
Disulfide	Count of disulfide bridges
Proximal pi	Count of fragments of carbon bonded to a sp2 atom
Carboxy	Count of carboxy groups
Carboxy E-neg	Count of carboxy groups bonded to an electronegative atom
Prox E-neg	Count of fragments of carbon bonded to an electronegative atom
Prox Halide	Count of fragments of carbon bonded to a halide
Vinyl Carboxy	Count of vinyl carboxy groups
Vinyl N	Count of vinyl nitrogen groups
Triple Bond	Count of triple bonded carbon

FIGURE 4A

Aromatic Model Descriptors

Conjug	Size of the conjugated system (aromatic + double bond systems)
ConjugEn	Total electronegativity values of immediate atom neighbors of the conjugated system
ConjugPC	Total partial charge values of immediate atom neighbors of the conjugated system
arC 1	Count of aromatic carbon one aromatic bond away
arC 2	Count of aromatic carbon two aromatic bonds away
arC 3	Count of aromatic carbon three aromatic bonds away
arC 4	Count of aromatic carbon four aromatic bonds away
arC 5	Count of aromatic carbon five aromatic bonds away
arC 6	Count of aromatic carbon six aromatic bonds away
arN 1	Count of aromatic nitrogen one aromatic bond away
arN 2	Count of aromatic nitrogen two aromatic bonds away
arN 3	Count of aromatic nitrogen three aromatic bonds away
arO 3	Count of aromatic oxygen three aromatic bonds away
Heavy 1	Count of neighbor heavy atom one aromatic bond away
Heavy 2	Count of neighbor heavy atom two aromatic bonds away
Heavy 3	Count of neighbor heavy atom three aromatic bonds away
E-neg 1	Count of neighbor electronegativity atom one aromatic bond away
E-neg 2	Count of neighbor electronegativity atom two aromatic bonds away
E-neg 3	Count of neighbor electronegativity atom three aromatic bonds away
C 1	Count of neighbor carbon one aromatic bond away
C 2	Count of neighbor carbon two aromatic bonds away
C 3	Count of neighbor carbon three aromatic bonds away
N 1	Count of neighbor nitrogen one aromatic bond away
N 2	Count of neighbor nitrogen two aromatic bonds away
N 3	Count of neighbor nitrogen three aromatic bonds away
O 1	Count of neighbor oxygen one aromatic bond away
O 2	Count of neighbor oxygen two aromatic bonds away
O 3	Count of neighbor oxygen three aromatic bonds away
S 1	Count of neighbor sulfur one aromatic bond away
S 2	Count of neighbor sulfur two aromatic bonds away
S 3	Count of neighbor sulfur three aromatic bonds away
pi 1	Count of neighbor sp2 atoms one aromatic bond away
pi 2	Count of neighbor sp2 atoms two aromatic bonds away
pi 3	Count of neighbor sp2 atoms three aromatic bonds away
Chg 0	Partial charge of the atom
Chg 1	Total partial charge of atoms one aromatic bond away
Chg 2	Total partial charge of atoms two aromatic bonds away
Chg 3	Total partial charge of atoms three aromatic bonds away

FIGURE 4B

Aliphatic Model Descriptor Coefficients

Descriptor	Coefficient
Const	11.03
Charge	-2.38
ConjSys	-0.05
ConjSysEn	-0.01
ConjSysPC	0.63
Fused	0.31
FuseStrain	2.80
3 Ring	2.18
4 Ring	0.94
5 Ring	0.46
6 Ring	-0.53
Dibenzylic	0.29
C	0.03
Aro C	-0.57
Dbl C	-0.72
N	-1.26
O	-0.01
Si	1.64
S	-0.56
C Ch	3.11
Aro C Ch	0.18
Dbl C Ch	8.43
N Ch	5.43
O Ch	0.29
Si Ch	27.40
S Ch	12.22
Eneg	-0.23
H	0.55
Tpl C	-0.63
Conj N	0.32
Aro N	1.25
Halide	0.50
2 Neighbor	-0.17
3 Neighbor	0.17
N pi	0.11
N E-neg	-0.30
Amide N Side	0.49
N S-Adjacent	-1.07
O pi	0.43
Aro Ether	0.31
Oxy Ester	0.58
Oxide	0.89
O E-neg	1.65
S E-neg	2.44
S 2 E-neg	2.44
Disulfide	-1.46
Proximal pi	0.41
Carboxy	0.44
Carboxy E-neg	0.31
Prox E-neg	0.32
Prox Halide	0.41
Vinyl Carboxy	1.27
Vinyl N	-0.77
Triple Bond	-0.63

FIGURE 5A

Aromatic Model Descriptor Coefficients

Descriptor	Coefficient
Const	12.95
Conjug	-0.03
ConjugEn	-0.01
ConjugPC	0.35
arC 1	-0.86
arC 2	-0.15
arC 3	-0.27
arC 4	-0.11
arC 5	-0.03
arC 6	0.00
arN 1	0.86
arN 2	-0.46
arN 3	-0.03
arO 3	-0.42
Heavy 1	0.03
Heavy 2	0.02
Heavy 3-	0.15
E-neg 1-	0.26
E-neg 2	0.06
E-neg 3	-0.15
C 1	0.26
C 2	-0.03
C 3	-0.10
N 1	-0.26
N 2	0.05
N 3	-0.19
O 1	-0.31
O 2	-0.12
O 3	-0.04
S 1	0.69
S 2	-0.09
S 3	-0.46
pi 1	0.30
pi 2	0.02
pi 3	0.02
Chg 0	5.50
Chg 1	-0.89
Chg 2	1.15
Chg 3	0.29

FIGURE 5B

Camitro - ADME Models - Microsoft Internet Explorer provided by EarthLink Network, Inc.

File Edit View Favorites Tools Help

Back Forward Stop Refresh Home Search Favorites History Mail Print Edit Discuss

Address https://websummit.camitro.com/jsp/regio_results.jsp?action=regio_results&jobcmpid=2166

Camitro

Home | Submit Compounds | View All Results | View Jobs In Progress | Logout

About This Beta Version | Readme | Acknowledgements

CONFIDENTIAL

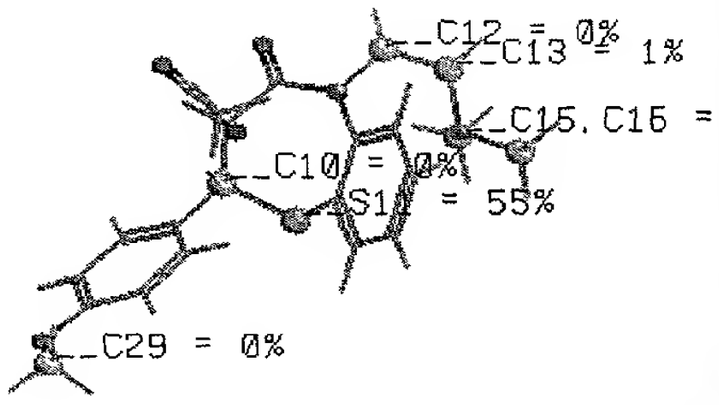
Greetings, Katrin Mackarehschian

Regio Results for DILTIAZEM

Mail Feedback

Return to previous Compounds List

For display issues, click the ? button

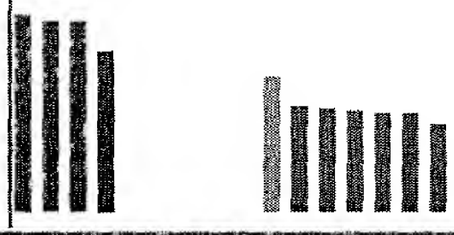


Regio Summary Table

Site	Ratio	Lability
S11	55%	Labile
C15,C16	44%	Labile
C13	1%	Labile
C29	0%	Mod Labile
C10	0%	Mod Labile
C12	0%	Mod Labile

Hetero Atoms On/Off. Reload Picture.

Metablolic Landscape



Done

Internet

Start | Exploring - D... | Inbox - Micr... | Returning Re... | Camitro | Redesign C... | List of Drugs | Untitled - Paint | 5:2

FIGURE 6

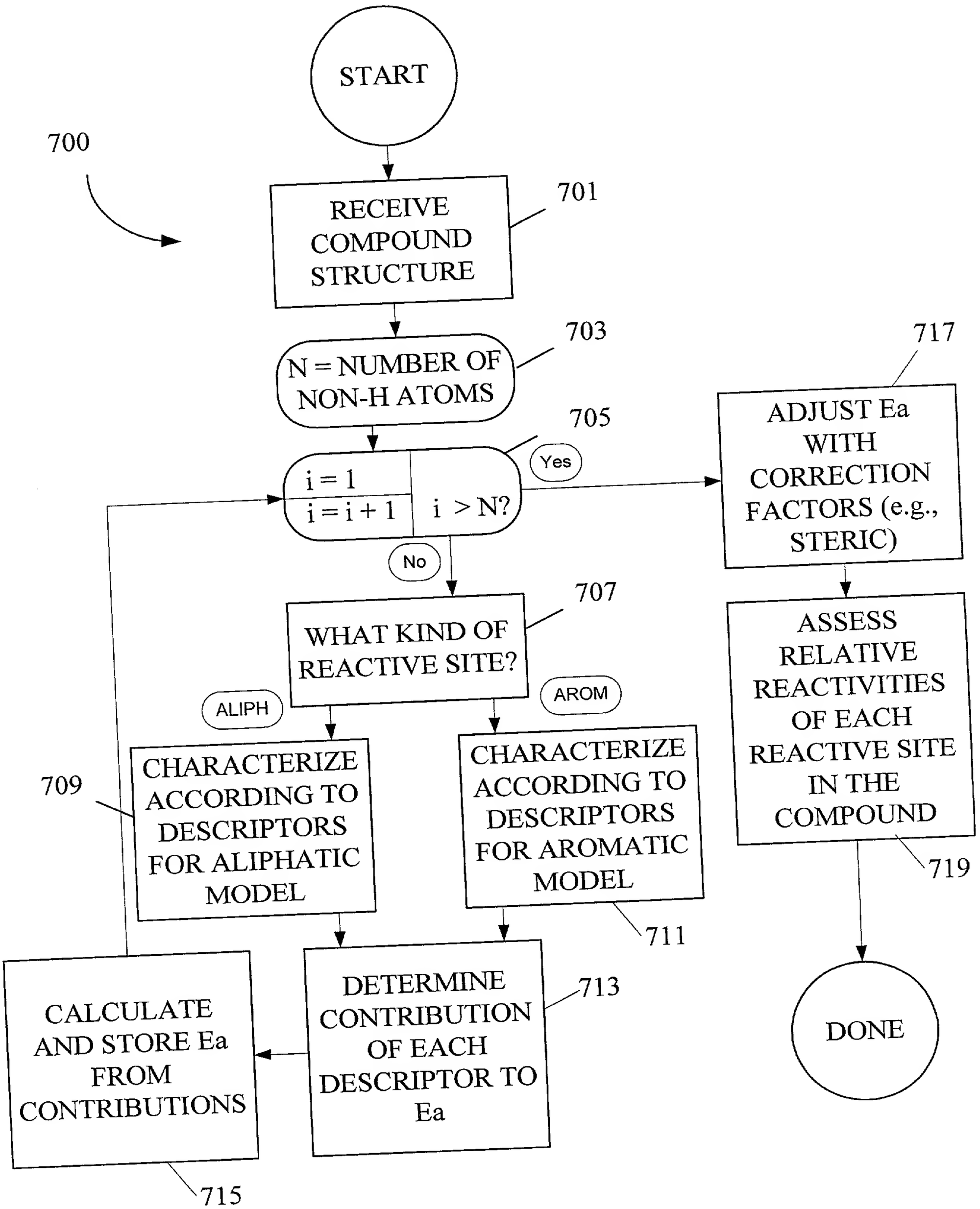

START
700
RECEIVE COMPOUND STRUCTURE
701
N = NUMBER OF NON-H ATOMS
703
i = 1
i = i + 1
i > N?
705
Yes
No
ADJUST Ea WITH CORRECTION FACTORS (e.g., STERIC)
717
WHAT KIND OF REACTIVE SITE?
707
ALIPH
AROM
CHARACTERIZE ACCORDING TO DESCRIPTORS FOR ALIPHATIC MODEL
709
CHARACTERIZE ACCORDING TO DESCRIPTORS FOR AROMATIC MODEL
711
ASSESS RELATIVE REACTIVITIES OF EACH REACTIVE SITE IN THE COMPOUND
719
DETERMINE CONTRIBUTION OF EACH DESCRIPTOR TO Ea
713
CALCULATE AND STORE Ea FROM CONTRIBUTIONS
715
DONE

FIGURE 7

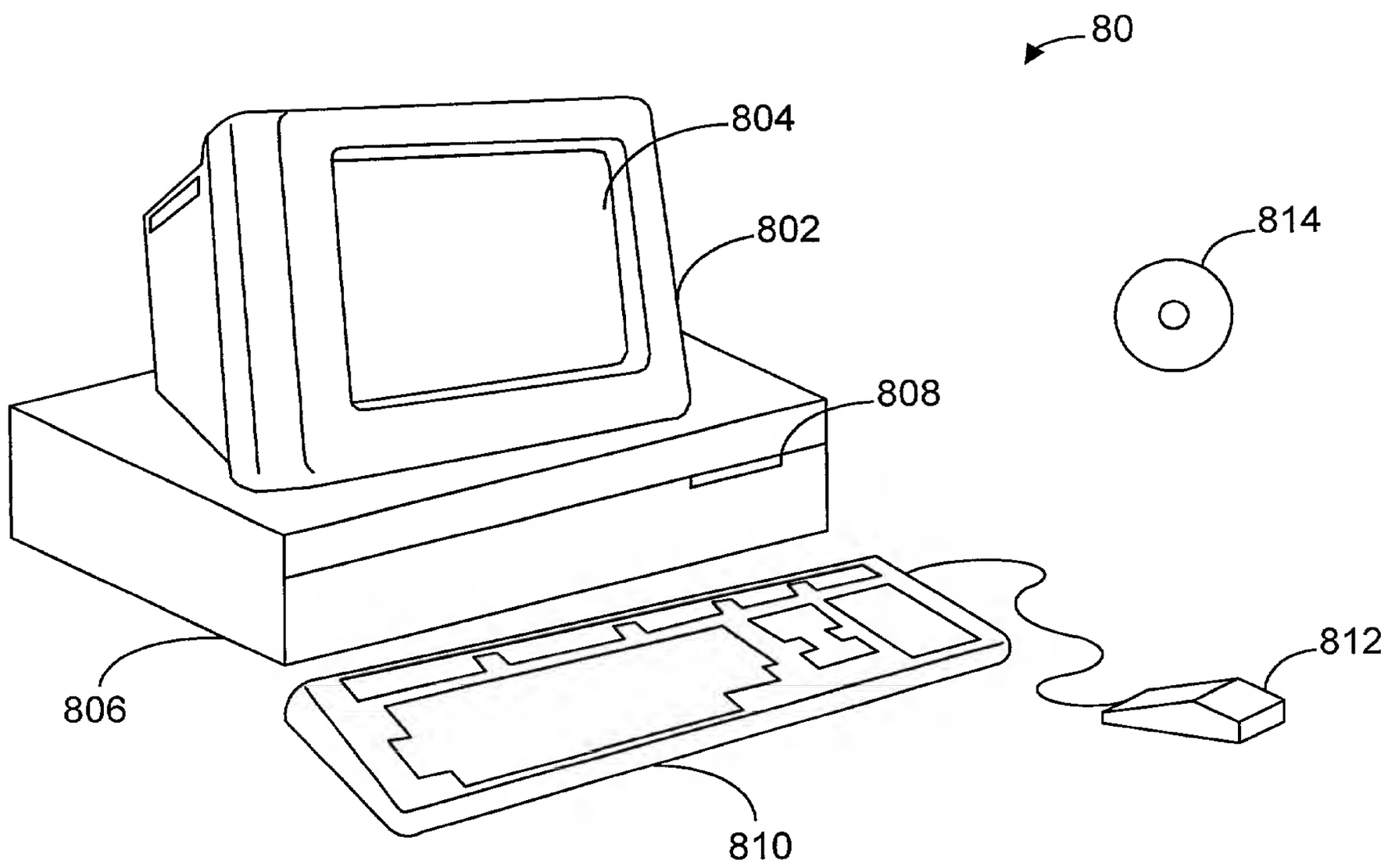


Figure 8A

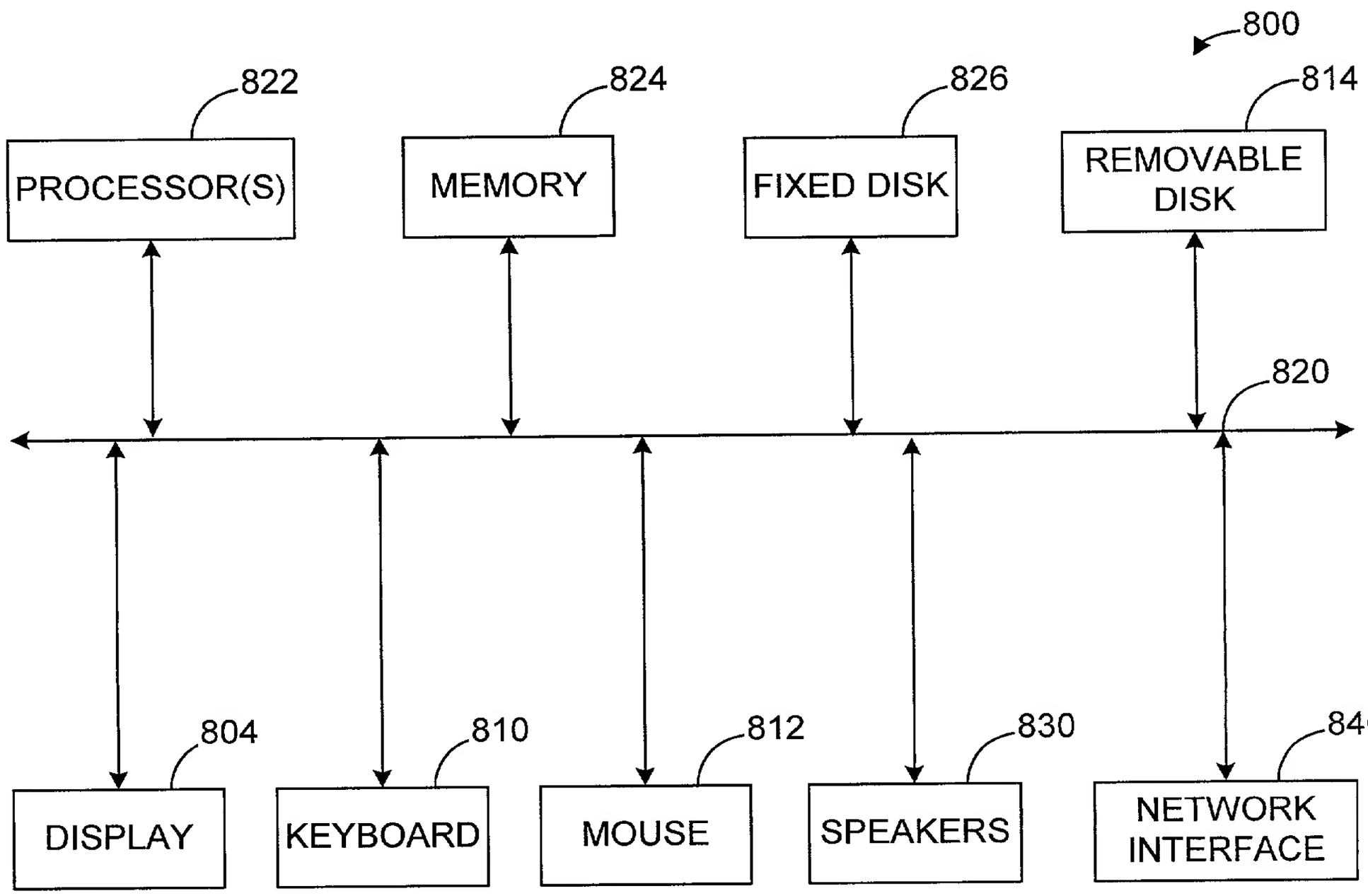


Figure 8B